



Real-life Evidence of Lower Lung Virulence in COVID-19 Inpatients Infected with SARS-CoV-2 Omicron Variant Compared to Wild-Type and Delta SARS-CoV-2 Pneumonia

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Abstract

In vitro and animal models described lower replication capacity and virulence of SARS-CoV-2 Omicron lineage in lower respiratory airways compared to wild type and other variants of concern (oVOCs). Among adult subjects admitted to our hospital (Turin, Italy) due to wild type, oVOCs, and Omicron SARS-CoV-2-related pneumonia ($n = 100$ for each lineage), the cases of Omicron pneumonia showed lower degree of lung parenchyma involvement ($a\beta -1.471$, $p = 0.037$), less tendency to parenchyma consolidation ($aOR 0.500$, $p = 0.011$), and better respiratory functions (assessed by ambient air arterial blood gas analysis). After adjusting for demographic, previous immunity, and comorbidities, Omicron pneumonia still associated with lower risk of respiratory failure (for severe respiratory failure, Wild-type versus Omicron $aOR 15.6$, $p = 0.005$ and oVOCs versus Omicron $aOR 31.7$, $p < 0.001$). These observations are in line with preliminary findings from in vitro and animal models and could explain why Omicron infection has been associated with lower mortality and hospitalization in human.

Keywords ARDS · SARS-CoV-2 · Virulence · Pneumonia · Omicron · Variants of Concern

Introduction

Soon after the beginning of COVID-19 pandemic SARS-CoV-2 variants have been selected. Variants of concern (VOCs) differ from wild-type virus (WT) in terms of transmissibility, potential of immune evasion, and adverse impact on diagnostics and therapeutics [1]. Delta (B.1.617.2) lineage appeared in October 2020: several amino acid substitutions in the spike protein (Sp) enhanced angiotensin-converting enzyme-2 (ACE2) binding, viral transmission, and immune evasion [1]. Omicron (B.1.1.529) lineage was identified in November 2021 presenting 37 substitutions in the Sp, half of which in the receptor-binding domain

[1]. There is increasing evidence from animal models and ex vivo studies that, compared to previous VOCs, Omicron possess significantly higher and lower replication competence and virulence in upper and lower respiratory airways, respectively [2–4]; this is probably due to the combination of enhanced binding to ACE2 receptor (more extensively expressed in bronchi and upper respiratory airways), higher independence on the transmembrane serine protease 2 co-receptor (differentially expressed in upper and lower respiratory airways), and different preferential mechanisms of cell entering [2–4].

Nevertheless, to date there are no in-human data that could attribute the extensive epidemiological evidence of reduced risk of hospitalization and death [5, 6] to the attenuated lung pathogenicity of Omicron observed in animals and in vitro models; furthermore, higher replication competence in the upper respiratory airways does not necessarily translate into lower degree of inflammation and cell injury in the lower respiratory airways once pneumonia develops. Any explanation of the clinical and epidemiological findings in human is further complicated by several confounding factors that affect the comparison of lung pathology between WT and other VOCs (oVOCs): previous immunization, the

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evolution of clinical management, as well as hardly quantifiable survival biases. Herein, we compared high-resolution computed tomography scan (HRCT) findings and the respiratory function of subjects who developed pneumonia after infection by WT/Omicron and oVOCs in the free time from any medical intervention (from the onset of COVID-19 signs and symptoms up to the linkage to care). Our hypothesis is that, even in the COVID-19 cases requiring hospitalization, Omicron pneumonia shows lower virulence and impairment of respiratory functions compared to WT and oVOCs.

Methods

We carried on a cross-sectional retrospective study comparing lung involvement and respiratory function at emergency department (ED) admission between WT, oVOCs, and Omicron pneumonia at our infectious diseases' unit (Amedeo di Savoia Hospital, Turin, Italy) in March–April 2020, October–December 2021, and February–May 2022, respectively. The first hundred adults hospitalized due to evidence of SARS-CoV-2 pneumonia at HRCT and with available data on respiratory functions in ambient air before any medical interventions were consecutively included. Lung involvement was quantified according to Ooi et al. [7]. Values of ambient air arterial blood gas analysis, respiratory frequency, and symptoms at the date of HRCT were collected from clinical records. HRCT was performed the same day of ED admission, when subjects sought medical care. Subjects with clinical, laboratory, or radiological evidence of bacterial superinfection, pulmonary embolism, or congestive heart failure were excluded. Subject with no blood gas data in ambient air were also excluded together with subjects that underwent any type of medical intervention at home (oxygen support, steroids, monoclonal, or antiviral therapies). These criteria have allowed us to focus on a condition mimicking SARS-CoV-2 physiopathology unbiased by medical interventions and adjusted by the time between the evaluation and the signs/symptoms onset. Respiratory failure was classified as mild (200 mmHg < partial pressure of oxygen-to-fraction of inspired oxygen ratio, P/F \leq 300 mmHg), moderate (100 mmHg < P/F \leq 200 mmHg), and severe (P/F \leq 100 mmHg), according to Ranieri et al. [8]. WT/oVOCs cases were diagnosed by standard RT-PCR. Considering viro-epidemiological data on VOCs circulating in Italy [9], most of the cases grouped as oVOCs should have belonged to Delta lineage. All the Omicron cases were confirmed through amplification failure of the spike gene (TaqPath CE-IVD RT-PCR). Analyses were adjusted for biologically relevant variables plus variables associating with SARS-CoV-2 lineage. The study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Inter-Department Ethics Committee A.O.U.

Città della Salute e della Scienza, A.O. Ordine Mauriziano di Torino, and A.S.L. Città di Torino (Torino, Italy, number 0065839–00,304/2020). Informed consent was obtained from all participants included in the study.

Results

As per study protocol, 300 subjects were included. Compared to WT and oVOCs pneumonia, participants developing pneumonia due to Omicron infection were older, more equally distributed between sexes, had higher prevalence of previous immunization (predominantly by vaccination) and comorbidities (mainly cancers, cardiovascular and neuropsychiatric disorders), and showed longer time from signs/symptoms onset to HRCT acquisition (Table.1). Despite no relevant difference in the number of lung parenchyma areas involved, Omicron pneumonia presented less commonly with consolidated lesions and associated with lower prevalence of respiratory failure, lower median respiratory rate, and higher median partial pressure of oxygen (PaO₂), P/F ratio, and arterial blood oxygen saturation (SpO₂; Table.1).

Moving from WT/oVOCs to Omicron pneumonia, the degree of P/F change was +63.5 (β 95%CI: 40.2; 86.8; $p < 0.001$). Accordingly, compared to Omicron pneumonia, WT and oVOCs pneumonia associated with increased risk of mild (ORs: 1.50 [0.80; 2.81] $p = 0.202$ and 4.05 [2.02; 8.11] $p < 0.001$), moderate (ORs: 6.24 [2.10; 18.59] $p < 0.001$ and 7.36 [2.23; 24.31] $p < 0.001$), and severe respiratory failure (ORs: 8.21 [1.67; 40.25] $p = 0.009$ and 16.87 [3.53; 84.84] $p < 0.001$), respectively. After adjusting for age, sex, time from COVID-19 onset to HRCT, vaccine doses, pulmonary, cardiovascular, and tumoral disease, P/F values independently associated with SARS-CoV-2 lineage (Omicron versus others: $a\beta + 28.36$ [12.04; 44.68], $p < 0.001$), number of vaccine doses ($a\beta + 13.43$ [1.88; 24.98], $p = 0.023$), and presence of cardiovascular disease ($a\beta -49.55$ [-74.45; -24.66], $p < 0.001$); similar independent associations were found at modeling multivariate analysis for the relationship between lineages and respiratory failure (Table.2).

Having observed nonstatistically significant difference in the parenchymal extension of pneumonia between the lineages, but significant differences in the type of consolidation involvement, we assessed whether Omicron infection could be less pathogenic even in the lung areas where pneumonia develops, maintaining higher degree of tissue functioning compared to WT/oVOCs. Fitting into the multivariate models the number of parenchymal areas and the type of pneumonia lesions lead to a loss of significance for the association of SARS-CoV-2 lineage with P/F and respiratory failure, revealing co-dependency between the lineages, the parenchyma volume involvement, and the type of lesions (data not shown). Bivariate analysis adjusted by the time

Table 1 Comparison of demographics, clinical presentation, HRCT findings, and respiratory functions at emergency department admission between WT, oVOCs, and Omicron infections

Variable	WT (n = 100)	oVOCs (n = 100)	Omicron (n = 100)	P	Omicron vs WT*	Omicron vs oVOCs*
Age, years	67 (56–77)	63 (52–79)	78 (64–83)	<0.001	0.001	0.001
Male sex, n	73	60	56	0.034	0.039	0.998
Caucasian ethnicity, n	88	89	94	0.307	0.455	0.697
Time from COVID-19 signs/symptoms onset to HRCT, days	6 (3–7)	6 (4–9)	6 (3–9)	0.006	0.090	0.998
Lung areas, number/24	11 (7–14)	10 (8–14)	8 (3–14)	0.100	0.100	0.609
Pneumonia type, n	61	57	74	0.033	0.168	0.037
Interstitial only	39	43	26			
Consolidation						
SpO ₂ , %	88 (72–96)	86 (66–95)	92 (88–97)	0.012	0.018	0.009
RR, n/min	18 (12–28)	20 (16–26)	18 (14–20)	0.027	0.463	0.022
PaO ₂ /FiO ₂	270 (192–370)	280 (211–324)	323 (277–399)	0.008	0.033	0.014
PaO ₂ , mmHg	56.7 (40.4–77.8)	58.8 (45.1–68.2)	67.9 (58.2–83.8)	0.009	0.033	0.017
Respiratory failure, n	28	15	46	<0.001	<0.001	<0.001
Absent (P/F > 350)	43	62	47			
Mild (200 < P/F ≤ 350)	19	12	5			
Moderate (100 < P/F ≤ 200)	10	11	2			
Severe (P/F ≤ 100)						
Symptoms, n	23	52	40	<0.001	0.041	0.244
Dyspnea	18	12	10	0.224	0.290	0.999
Headache	15	39	41	<0.001	<0.001	0.998
Cough	24	4	25	<0.001	0.069	0.175
Runny nose	28	6	16	<0.001	0.999	<0.001
Pharyngitis	45	62	34	<0.001	0.359	<0.001
Fever						
Vaccinated, n	0	29	58	<0.001	<0.001	0.003
mRNA doses	0 (0–0)	0 (0–1)	2 (0–3)	<0.001	<0.001	<0.001
Positive anti-S1/S2 IgG ^o	0	0	5	0.006	0.017	0.017
Comorbidities/subject	1 (1–2)	1 (1–2)	2 (2–3)	0.007	0.009	0.097
Comorbidities, n	47	44	63	0.016	0.072	0.022
CVDs	13	14	25	0.046	0.076	0.121
Neuropsychiatric	40	32	46	0.127	0.999	0.129
Pulmonary	8	11	23	0.005	0.007	0.044
Cancer	13	18	14	0.579	0.999	0.999
Overweight	11	11	17	0.347	0.624	0.624
Diabetes	10	6	15	0.112	0.739	0.111
CRF	7	7	12	0.350	0.629	0.629
Immune disorders	11	8	10	0.766	0.999	0.999
Hepatic						
COVID-19-related mortality, n	21	25	7	0.002	0.008	0.001

Legend: WT, wild-type SARS-CoV-2; oVOCs, other variants of concerns (mainly Delta lineage); HRCT, high-resolution computed tomography; SpO₂, arterial blood oxygen saturation; RR, respiratory rate; PaO₂, partial pressure of oxygen; FiO₂, fraction of inspired oxygen; P/F, partial pressure of oxygen-to-fraction of inspired oxygen ratio; CVDs, cardiovascular disorders; CRF, chronic renal failure. ^oAmong unvaccinated, anti-S1/S2-spike IgG were available for all the admissions due to oVOCs and Omicron; WT were deemed as seronegative

*Two-by-two comparisons underwent Bonferroni/Yates correction to reduce multiple testing bias and p-values were reported accordingly.

from symptoms onset to HRCT acquisition confirmed that the lineages differed also for the extension of lung parenchyma involvement (Omicron versus WT/oVOCs $a\beta -1.471 [-2.853; -0.089]$, $p = 0.037$) and tendency to consolidation (Omicron versus WT/oVOCs $aOR 0.500 [0.294-0.850]$, $p = 0.011$).

Discussion

After adjusting for demographic, comorbidities, time from disease onset, and previous immunity, we observed that, compared to WT and oVOCs infections, Omicron infection was associated with lower risk of respiratory failure

Table 2 Multinomial logistic regression for respiratory failure risk at hospital admission according to SARS-CoV-2 lineages and other univariate relevant factors

Respiratory failure	Variable	aOR (95%CI)	P
Mild vs none	Vaccine doses	0.77 (0.58–1.023)	0.077
	Sex (ref.female)	0.94 (0.52–1.71)	0.843
	Age	0.99 (0.98–1.02)	0.753
	Time from COVID-19 to evaluation	1.03 (0.96–1.11)	0.402
	Cardiovascular diseases (ref. none)	1.88 (1.03–3.41)	0.039
	Lung diseases (ref. none)	3.27 (1.76–6.08)	<0.001
	Cancer (ref.none)	1.14 (0.47–2.77)	0.778
	SARS-CoV-2 lineage, Omicron (ref.)	1.41 (0.61–3.25)	0.425
	WT	4.69 (2.09–10.55)	<0.001
	oVOCs	–	–
Moderate vs none	Vaccine doses	0.46 (0.23–0.91)	0.025
	Sex (ref.female)	1.31 (0.52–3.35)	0.566
	Age	1.01 (0.98–1.04)	0.588
	Time from COVID-19 to evaluation	1.09 (0.98–1.22)	0.124
	Cardiovascular diseases (ref. none)	2.15 (0.90–5.11)	0.084
	Lung diseases (ref. none)	2.99 (1.24–7.24)	0.015
	Cancer (ref.none)	2.71 (0.81–9.05)	0.106
	SARS-CoV-2 lineage, Omicron (ref.)	5.58 (1.46–21.29)	0.012
	WT	9.36 (2.41–36.36)	0.001
	oVOCs	–	–
Severe vs none	Vaccine doses	0.95 (0.49–1.83)	0.880
	Sex (ref.female)	0.43 (0.15–1.19)	0.103
	Age	0.99 (0.96–1.03)	0.616
	Time from COVID-19 to evaluation	1.01 (0.88–1.17)	0.887
	Cardiovascular diseases (ref. none)	10.44 (3.08–35.38)	<0.001
	Lung diseases (ref. none)	1.84 (0.61–5.59)	0.282
	Cancer (ref.none)	2.37 (0.56–10.06)	0.242
	SARS-CoV-2 lineage, Omicron (ref.)	15.60 (2.26–107.78)	0.005
	WT	31.74 (5.27–191.03)	<0.001
	oVOCs	–	–

Legend: aOR, adjusted Odds ratio; 95%CI, 95% confidence interval for aOR; WT, wild-type virus; oVOCs, other variant of concerns, mainly Delta lineage.

and impairment of respiratory exchanges at the time of hospitalization for SARS-CoV-2 pneumonia. After a median time of 6 days from signs/symptoms onset and no treatment, the better respiratory function in Omicron pneumonia was associated with lower tendency to early parenchymal consolidation, lower degree of lung parenchyma involvement, and higher P/F ratios, whereas it was independent from other relevant factors known to be able to affect the evolution and severity of SARS-CoV-2 infection such as age, comorbidities, and immunity [10, 11]. As for the last factor, our study was underpowered to properly assess the effects of both natural- and vaccine-elicited immunity, as the number of subjects with previous immunity due to natural infection was extremely low ($n=5$). Further limitations of our study include the small sample size, the retrospective design, and the inability to differentiate among sub-lineages of Omicron

as well as among the lineages grouped as oVOCs. Lastly, our observations refer to the first median 6 days only of overt symptomatic COVID-19 and excluded further evolutions; thus, we cannot strictly prove that SARS-CoV-2 lineages have independently affected the different mortalities between Omicron and other lineages that we have also observed in our study population. Nevertheless, this temporal framework was chosen on purpose due to the interest in assessing the lung physiopathology of SARS-CoV-2 lineages in the absence of any medical intervention and therefore dictated by the ethical urgency of providing care when necessary.

These real-life observations are an *in vivo* preliminary confirmation of what has been described in animal models [2–4]. While the differential mortality associated with different SARS-CoV-2 lineages may depend on several hypothetical mechanisms (such as a different sensitivity to antivirals

and monoclonals or a different tendency to cause thrombotic complications), we described one of these potential reasons. Indeed, this is the first in-human detailed description of milder air functioning impairment and lower lung virulence of Omicron variant that could explain on a pathophysiological basis the lower mortality and hospitalization rates associated with Omicron and observed by larger cohort studies [5, 6]. Further data are required to confirm our observation and to assess whether the lower pulmonary virulence possessed by Omicron variant during the first week of symptomatic disease remains so in the following weeks, as suggested by the overall lower mortality in the Omicron group compared to the others. Human pathology data able to describe the interactions between omicron variant and airways cells receptors underlying our radiological and physiological results are also warranted to identify potentially therapeutic molecular targets.

Author Contributions MT, AC, GDP, SB, and GC contributed to the study conception and design. Material preparation, data collection, and analysis were performed by MT, FP, SV, PN, and FT. The first draft of the manuscript was written by MT and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Declarations

Competing interest The authors declare no competing interests.

Conflict of interest The authors have no relevant financial or non-financial interests to disclose.

Ethical Approval This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Inter-Department Ethics Committee A.O.U. Città della Salute e della Scienza, A.O. Ordine Mauriziano di Torino, and A.S.L. Città di Torino (Torino, Italy, number 0065839–00304/2020).

Consent to Participate Informed consent was obtained from all individual participants included in the study.

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